

Investigating Pain, Touch, and Temperature Sensations: Is a small fiber sensory and autonomic neuropathy part of the syndrome?

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Many parents and family members of children and adults with Cornelia de Lange Syndrome (CdLS) have experienced and observed similar phenomena: The affected individual seems to have an apparent indifference to pain or a high pain threshold, or vice versa there may be unexplained bouts of pain or discomfort that is hard to localize. Or the skin in the extremities is overly blotchy and there may be abnormalities of sweating. And then there is the common problem of gastro-esophageal (GE) reflux. What could be underlying all of this? Some of these features are suggestive of the symptoms seen in disorders that involve small diameter nerves that are involved in the perception of pain and temperature as well as in regulating autonomic (vegetative) nervous system functions.

So what are these small nerve fibers, what is their role, and what happens if there is a problem with these nerves?

The nerves that transmit sensory information back to the human brain come in different sizes and are specialized to pick up different kinds of sensory information. Large nerve fibers have thick layers of insulation around them (the myelin sheet) that give them the ability to conduct nerve impulses very quickly. These thick fibers transmit sensory information such as the perception of light touch on the skin and the sense of knowing where the limbs are in space (proprioception). In contrast, the small fibers conduct information much more slowly because they have only very thin sheets of myelin around them or even have no myelin at all. These fibers transmit different kinds of sensory information including pain, the ability to feel hot or cold temperature, and deeply applied pressure. This slowness of conduction is the reason why there often appears to be a lag time between touching a hot surface and when we actually perceive the heat. The fibers with thin myelin are called "A delta fibers." They are responsible for the transmission of cold perception and pain sensation in the skin. The fibers without any myelin are referred to as "C fibers" and transmit heat sensation as well as pressure. Small diameter myelinated (insulated) and unmyelinated (not insulated) fibers are also used by the so-called vegetative or autonomic nervous system. The autonomic nervous system is involved in all visceral functions, from controlling blood pressure and heart rate to regulating the muscles of the digestive tract and bladder as well as regulating sweat production and blood perfusion of the skin. In a disease of small diameter nerves some or all of these functions can be affected; hence, the typical collection of symptoms that is often observed in these disorders.



A frequent symptom in sporadic small fiber sensory neuropathies is spontaneous pain (neuropathic pain) that is often perceived as burning. In addition, individuals may feel unpleasant sensations such as tingling and “pins and needles” often leading to an urge to move the extremity or to shake it and have it massaged. However, a subset of patients experience unpleasant sensations evoked even by lightly touching their skin, resulting again in a burning and painful sensation (referred to as dysaesthesias). Vice versa, they may also have decreased pain perception, decreased temperature perception, self-mutilation, ulcerations and other painless injuries. Problems with the autonomic nervous system may lead to problems maintaining blood pressure when standing up (orthostatic hypotension), fainting spells (syncope), decreased tear production, decreased sweat production (anhidrosis), and problems with gut motility (the passing of food through the stomach and intestines).

Skin discoloration: Is it Raynaud’s phenomenon?

The mottling of the skin (a meshwork-like discoloration of the skin) is different from the well-known Raynaud’s phenomenon. In Raynaud’s phenomenon there is an overreaction of the blood vessels in the skin when exposed to a cold environment. The typical sequence of events is for fingers or toes to turn white upon the exposure to cold, followed by a blue and finally red discoloration. The whiteness results from a lack of bloodflow to the fingers, the blue from the relative lack of oxygen in the fingers and the red signals the end of the episode when there is increased blood flow to the fingers again, turning them red and hot. The cause for the Raynaud’s phenomenon often is not known. It may occur in isolation, but it can also be a sign of inflammation of the vessels as can be seen in some rheumatological conditions. Neuropathies (primary disorders of the nerves) are not a typical cause for true Raynaud’s, and more often it is just the exaggerated mottling and not a true Raynaud’s phenomenon that is seen in neuropathies that specifically affect the small fiber.

What can cause a disease of the small diameter nerve fibers?

Most of the time, small fiber neuropathies arise in adults without apparent cause, although they are an important complication of diabetes. A small-fiber neuropathy can also occur as an autoimmune phenomenon or as a result of exposure to certain medications and toxins. There are some well-known genetic entities in which small fiber neuropathies are a major part of the picture, all of which are very rare. One of them is the Riley-Day Syndrome, also known as familial dysautonomia, which is associated with impaired blood pressure regulation, reduced tear production, impaired pain sensation, preserved sweating, and absent fungiform papillae on the tongue. There also is another familial form, in which the patient is unable to produce sweat and there also is a congenital insensitivity to pain with self-mutilation, as well as often some degree of mental retardation, the cause of which is unclear.



Is there a small fiber neuropathy in CdLS also?

As noted at the beginning, some of these symptoms sound reminiscent of what is sometimes seen in persons with CdLS. Dr. Anthonie Kline and Dr. Laird Jackson picked up on these observations and tried to verify this in a larger group of patients by sending out a questionnaire to CdLS families. The results were quite suggestive: 90% responded that the individual with CdLS in their family appeared to at least react differently to pain, 60% observed blotching of the skin, 57% and 56% appeared to react differently to cold and heat respectively, 52% had decreased tear production, while 11% even had absent tear production.

This would suggest that perhaps there indeed is a small-fiber neuropathy that is part of the many symptoms that can occur in CdLS. How could this be studied further to objectify the preliminary findings? Regular nerve conduction velocity studies done in the neurological practice often will not be useful as they are measuring the large and fast conducting fibers only and miss the contributions of the small fibers. Nonetheless, it would be worthwhile to start with this easily available test, because if abnormalities were found on this test that would certainly be quite suggestive of problems with the peripheral nerves in general. However, one of the best ways to get a look at the function of the small fiber nerves themselves is to look at the way the sweat glands in the skin react to nerve stimuli, because this effect is mediated by the small fibers of the autonomic nervous system. That can, for instance, be done by applying a chemical through the skin that sets off signals in those small nerves, and then measuring whether the sweat glands are turned on as result. This type of test requires a special instrument that is not commonly available. In the *intra-dermal histamine injection test* a chemical is injected into the superficial skin and a local flush that is mediated by the local small diameter nerves is scored. This test has the advantage of being very easy to perform, but unfortunately it is not very sensitive. Other testing methods would be less practical for patients with CdLS as they rely on the cooperation of the individual that is being tested, such as determining sensory thresholds to temperature or painful stimuli. In addition, one can also measure other aspects of the autonomic nervous system, such as looking at how the heart rate behaves over a period of time. Finally, it is now possible to take a direct look at the small nerve endings in the skin by performing a small skin biopsy and examining the skin under the microscope using special stains. We are currently planning to perform some of this testing on selected individuals with CdLS to see whether the notion that there may be a small fiber neuropathy in CdLS is holding up.

If there indeed is a neuropathy of the small diameter nerves in CdLS, how could that be influenced by treatment?

Unfortunately there is currently no treatment that would fix those small nerves and make them work again. All available treatment is symptomatic. For patients with neuropathic types of pain (those patients who are not insensitive to pain, but rather suffer from spontaneous pain or have unpleasant spontaneous sensation), there are now



quite effective medications such as Gabapentin (Neurontin), Topiramate (Topamax), Carbamazepine (Tegretol), Amitriptylene and others. Gabapentin, Topiramate and Carbamazepine are usually used for the control of seizures, but surprisingly they are effective in the context of neuropathic pain as well. That is probably a reflection of their ability to stabilize the excitability of nerve cells in a more general sense. If one knew that this type of pain can occur in patients with CdLS, the physician would probably prescribe these medications more readily in situations where there appears to be unexplained discomfort or pain.

It is entirely conceivable that certain behaviors that may occur in patients with CdLS such as irritability and aggression may be, if not caused by, then perhaps aggravated by unrecognized painful sensations. If this is true, effective treatment of the neuropathic pain should improve that behavior also. Of course, it is vitally important to investigate for other causes of discomfort first, such as GE reflux disease. Patients with wide fluctuations in blood pressure or fainting spells because of drop in blood pressure when getting up can also be treated with effective medication. The insensitivity to pain seen in some forms of neuropathy cannot be effectively treated by medication. In severe cases of this insensitivity there is a risk for sustaining unnoticed injuries in particular to the fingers or toes as well as a tendency for self-mutilation. Such wounds may heal very slowly because small-diameter nerve fibers are involved in this healing process as well. One can try to prevent this by making sure that shoes are not too tight fitting so that pressure sores are avoided.

Clearly the question of a small fiber neuropathy in CdLS warrants further investigation as this finding may help to highlight new treatments that have not yet been explored.

